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12. (Amended) The method of claim 1, wherein the ADNF polypeptide is a mixture of ADNF I polypeptide of part (a) and the ADNF III polypeptide of part (b).

REMARKS

With this amendment, claims 1-18 are pending in the present application and are currently under examination. Claims 19-44 are currently withdrawn from consideration as being drawn to non-elected inventions. For convenience, the Examiner's rejections are addressed in the order presented in the October 20, 2001 Office Action.

Status of the claims

Support for the claim amendments can be found throughout the specification, claims and drawings, as originally filed. For example, claim 1 as amended by essentially incorporating the elements of claims 2 and 3. Claims 2, 3 and 12 were amended to provide proper antecedent basis for certain phrases. These amendments do not introduce any new matter.

Rejection under 35 U.S.C. §112, first paragraph: written description

Claims 1-3, 12 and 14 were rejected as allegedly containing subject matter which was not described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. According to the Examiner, "[w]ith the exception of SEQ ID NOS: 1-2 and 21-26, the skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acid and amino acids and therefore conception is not achieved until reduction to practice has occurred . . . ." In support of this position, the Examiner cites *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). The Examiner concludes that the remaining sequences encompassed by the claims fail to meet the written description requirement.

As an initial matter, Applicants note that to expedite prosecution, Applicants have amended claim 1 by adding the elements of claims 2 and 3 to further clarify the chemical structures of the claimed ADNF polypeptides. To the extent that the rejection applies to the amended claims, Applicants respectfully traverse. The claims meet the requirements for claiming a genus of polypeptides, as recited, e.g., in *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). Furthermore, there is no requirement in the patent law that, to meet the written

description requirement for a method claim, all species used in the method be explicitly recited in the specification.

A. The present invention meets the written description requirement for claiming a genus of polypeptides

As described by the Federal Circuit in *University of California v. Eli Lilly & Co.*, "[a] description of a genus of cDNAs may be achieved by means of . . . a recitation of structural features common to the members of the genus . . . ." *University of California*, 43 USPQ2d at 1406. Furthermore, the court in *Fiers v. Revel* stated that an adequate written description "requires a precise definition, such as by structure, formula, chemical name, or physical properties." *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993).

Here, the specification describes a genus of ADNF I polypeptides, wherein members of the genus all have an active site that confers biological activity. As described in WO96/11948 and U.S. Patent No. 6,174,862, the present inventors previously discovered full length ADNF I polypeptide and its active core site. This active site, which is only nine amino acids in length, is more potent than the full-length ADNF I polypeptide and is more effective over a greater range of concentrations (*i.e.*, from 0.01 fM to about 1 pM). The sequence of the nine amino acid active site is "SALLRSIPA" and it retains the biological activity of a full-length growth factor. Moreover, other ADNF I polypeptides that contain this active site also possess the biological activity of full-length ADNF I polypeptide. As such, the genus of ADNF I polypeptides share the common physical property of the core structure (*i.e.*, "SALLRSIPA"). Accordingly, the description of presently recited ADNF I polypeptides is sufficient evidence of possession of the claimed genus, because the genus is defined by a description of its physical properties, and because the genus is defined in relation to the structure of the core active site provided in claim 1.

Similarly, the specification also describes a genus of ADNF III polypeptides, wherein members of the genus all have an active site that confers biological activity. As described in WO98/35042 and U.S. Application No. 09/187,330, the present inventors previously discovered full length ADNF III polypeptide and its active site. This active site, which is only eight amino acids in length, has a sequence of "NAPVSIPQ" and it retains the biological activity of a full-length growth factor. Moreover, other ADNF III polypeptides that contain this active site also possess the biological activity of full-length ADNF III polypeptide. As such, this genus of ADNF III

polypeptides all shares the common physical property of the core structure (*i.e.*, "NAPVSIPQ"). Accordingly, the description of presently recited ADNF III polypeptides is sufficient evidence of possession of the claimed genus, because the genus is defined by a description of its physical properties, and because the genus is defined in relation to the structure of the core active site provided in claim 1.

Applicants further note that U.S. Patent No. 6,174,862 was issued to the present inventors with claims which define a genus of ADNF I polypeptides by the active site, as shown in present claim 1. If the ADNF I polypeptides as recited in claim 1 of U.S. Patent No. 6,174,862 meet the written description requirement of 35 U.S.C. §112, first paragraph, the ADNF I polypeptides as recited in the present claims must also meet the written description requirement.

B. There is no requirement in the patent law that all species used in the claimed method be explicitly recited in the specification

Fiers and *Amgen Inc.* addressed whether the applications at issue had sufficient written description to claim a genus of nucleic acids. The claims at issue in the instant application, however, are based at least in part on the surprising discovery that ADNF polypeptides can be used to reduce a condition associated with fetal alcohol syndrome in a subject who is exposed to alcohol *in utero*. Thus, the present invention is not directed to the discovery of new genus of nucleic acids or polypeptide (as were the cases in *Fiers* and *Amgen Inc.*). The genus of ADNF polypeptides encompassed by the present claims was already known (*see, e.g.*, WO96/11948 and WO98/35042). Rather, the present invention is directed to the use of known polypeptides in a novel and non-obvious way, *i.e.*, treatment of fetal alcohol syndrome.

Applicants respectfully submit that the holding in *In re Herschler,* 200 USPQ 711 (C.C.P.A. 1979) is more appropriate to analyze the present claims. In that case, the court specifically held that rejections for undue breadth and lack of written description were improper for claims relating to the use of DMSO to enhance tissue penetration of steroids. The claims were directed to the delivery of a genus of physiologically active steroids, while the specification provided one example demonstrating the efficacy of the claimed methods. The court reversed the Patent Office's rejection of these claims, reasoning that, because the invention was not the discovery of novel steroidal agents but a method of delivering the agents in combination with DMSO, explicit

written disclosure of all steroidal agents was not required to meet the written description requirement.

Similarly, in the present case, the claimed invention is not the discovery of particular ADNF polypeptides, but the discovery of novel methods of using them to confer reduction of a condition associated with fetal alcohol syndrome in a subject who is exposed to alcohol *in utero*. Based on this case law, it is clear that Applicants need not provide additional sequence information for other ADNF polypeptides to properly support the claims. In light of the clear guidance provided by the court on this issue, this rejection is improper and should be withdrawn.

Finally, Applicants respectfully remind the Examiner that the specification need not disclose all species encompassed by the claimed invention to satisfy the written description requirement of 35 U.S.C. §112, first paragraph. As clearly stated by the Court of Appeals for the Federal Circuit, "[a] specification may, within the meaning of §112, ¶ 1, containing a written description of a broad genus without describing all species that claim encompasses." *Utter v. Hiraga*, 6 USPQ2d 1709 (Fed. Cir. 1988). *See, also, University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398, 1405 (Fed. Cir. 1997). If "all" species encompassed by the claims must be described to satisfy the written description requirement, no generic claim would ever be allowable.

For the above reasons, Applicants believe that the written description requirement for ADNF I and ADNF III polypeptides as recited in the present claims is fully met. Accordingly, withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph: enablement

Claims 1-18 were rejected as allegedly lacking enablement. According to the Examiner, the claims are not enabled for the following reasons: A) the specification teaches treatment of animals with ADNF polypeptides NAP and SAL *prior to* exposure to alcohol, but does not show that the ADNF polypeptides affect a condition associated with fetal alcohol syndrome contracted *in utero* by exposure to alcohol; B) the specification fails to provide adequate guidance to the skilled artisan to test with reasonable probability the effect of the claimed peptides on any condition associated with fetal alcohol syndrome; C) the specification does not provide any guidance for the amount of an ADNF polypeptide sufficient to reduce a condition associated with fetal alcohol syndrome; D) it would require undue experimentation to identify other ADNF polypeptides that are

capable of alleviating conditions associated with fetal alcohol syndrome; and E) the specification does not provide adequate guidance for delivery of nucleic acids *in vivo*.

Applicants respectfully traverse the rejection. Each ground of the rejection is separately addressed below.

A. The claims encompass treatment of mammals exposed to alcohol *in utero*, by administering ADNF polypeptides

At pages 5-6 of the Office Action, the Examiner states the following:

> The specification teaches pretreatment of animals with ADNF polypeptides NAP and SAL ***, **prior to** exposure to alcohol... However, the protocol fails to support a reduction in a condition associated with fetal alcohol syndrome, which syndrome indicates a developed condition as claimed. In other words, the specification fails to show that the injected peptides affect a condition associated with fetal alcohol syndrome contracted *in utero* by exposure to alcohol as claimed. The experimental animals lack affliction with fetal alcohol syndrome because the animals lack prior exposure to alcohol.

Applicants respectfully traverse. The present claims are directed to a method for reducing a condition associated with fetal alcohol syndrome in a subject who is exposed to alcohol *in utero*, by administering ADNF polypeptides at any suitable stage. The ADNF polypeptides of the invention were tested and found to be effective in an art accepted model of fetal alcohol syndrome. According to the MPEP, "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." MPEP § 2164.02.

As described in the specification, ADNF polypeptides were tested using an art accepted model for fetal alcohol syndrome according to Webster *et al., Neurobehav. Tox.* 2:227-234 (1980) (see specification, page 32, line 27-28 and page 34, lines 22-33). ADNF polypeptides were administered 30 minutes prior to alcohol exposure of the subject *in utero*. Compared to control animals that were exposed to alcohol *in utero* without exposure to ADNF polypeptides, the treated animals showed a reduction in various conditions associated with fetal alcohol syndrome as shown in Figures 1, 2a, 2b and 3 (*e.g.*, fetal death, reduced fetal weight, reduced fetal brain weight, and reduced VIP mRNA level). Without the treatment with ADNF polypeptides, these animals would have otherwise fully developed these conditions associated with fetal alcohol syndrome as shown in

control. Accordingly, the present specification provides methods for reducing a condition associated with fetal alcohol syndrome in a subject who is exposed to alcohol *in utero*.

B. The specification provides guidance to develop and test the effect of ADNF polypeptides in animal models that are accepted in the art

At page 6 of the Office Action, the Examiner cites Hannigan *et al.* and states that fetal alcohol syndrome and alcohol-related neurodevelopmental disorders are characterized by life-long compromises in learning, memory and adaptive responses. The Examiner further states that the specification lacks the guidance required by the skilled artisan to develop and test the effect of the claimed polypeptides for any condition associated with fetal alcohol syndrome including compromises in learning, memory and adaptive response.

Applicants respectfully traverse. As identified in the Patent Office and the Federal Circuit, whether undue experimentation is required by one skilled in the art to practice to invention is determined by considering factors such as the amount of guidance presented in the application, the state of the prior art, and the presence of working examples. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1985); *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). As described in *Wands*, a "considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should precede." *Wands*, 8 USPQ2d at 1404 (quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982).

As described above, the specification provides an animal model for testing ADNF polypeptides for treatment of fetal alcohol syndrome. The present specification further demonstrates that ADNF polypeptides are effective in reducing conditions associated with fetal alcohol syndrome, *e.g.*, fetal death, reduced fetal weight, reduced fetal brain weight, and reduced VIP mRNA level (*see, e.g.*, Figures 1, 2a, 2b and 3 and page 7, lines 17-18). In addition, fetal alcohol syndrome is associated with other characteristics such as compromises in learning, memory and adaptive responses. Applicants have therefore provided ample guidance and working examples to test the effect of ADNF polypeptides on these and other conditions. The specification need not describe results for all conditions associated with fetal alcohol syndrome. However, the Examiner appears to be concerned about potential inoperative embodiments. Irregardless of this possibility, on the basis of their discovery Applicants are entitled to a reasonable scope of protection:

> Depriving inventors of claims which adequately protect them and limiting them to claims which practically invite appropriation of the invention while avoiding infringement inevitably has the effect of suppressing disclosure. What the dissent seems to be obsessed with is the thought of catalysts which *won't* work to produce the intended results. . . . Without undue experimentation or effort or expense the combinations which do not work will be readily discovered . . . . *In re Angstadt and Griffin*, 190 USPQ 214, 219 (C.C.P.A. 1976).

Accordingly, the rejection is improper and should be withdrawn.

C. A specific amount sufficient to reduce the condition associated with fetal alcohol syndrome need not be recited in the claims

At page 7 of the Office Action, the Examiner states that the claims fail to specify administration of any specified amount of ADNF polypeptide for treatment of a condition associated with fetal alcohol syndrome. Then, the Examiner concludes that the undue experimentation would be required for a skilled artisan to determine the amount of ADNF polypeptides required to produce such effect.

Applicants respectfully traverse. The first paragraph of 35 U.S.C. §112 has never been interpreted to require recitation of a specific dosage amount for claimed methods in the claims. The proper test of enablement is "whether one skilled in the art could make or use the claimed invention from the disclosure in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). MPEP §2164.01.

In the instant case, the specification provides guidance for selecting a suitable amount of ADNF polypeptides to reduce a condition associated with fetal alcohol syndrome. As described at page 25, lines 15-18, the specific amount effective for use will depend on various factors, such as the particular ADNF I or ADNF III polypeptide employed, the manner of administration, the weight and general health of the patients. For example, "an amount of ADNF I or ADNF III polypeptides falling within the range of a 1 μg to 50 μg, preferably 1 μg to 10 μg dose given intranasally once a day per mouse (*e.g.*, in the evening) would be a therapeutically effective amount. This dose is based on the average body weight of a mouse. Therefore, an appropriate dose can be extrapolated for a human body." *See* page 25, lines 19-23 of the specification. Applicants respectfully submit that based on the information provided in the specification coupled with information well known to those

skilled in the art, one of ordinary skill would be able to determine a suitable dosage of ADNF polypeptides for administration without undue experimentation.

D. Suitable ADNF polypeptides for the claimed methods can be determined without undue experimentation

At page 7 of the specification, the Examiner cites Skolnick *et al.* (*Trends in Biotech.* 18(1):34-39 (2000), and states that the skilled artisan recognizes the unpredictability in the art associated with the prediction of peptide function based upon divergent structure. Based on Skolnick *et al.*, the Examiner concludes that it would require undue experimentation for one of ordinary skill in the art to discover various ADNF peptides that possess the properties of alleviating conditions associated with fetal alcohol syndrome.

Applicants respectfully traverse and submit that the problems discussed in the reference cited by the Examiner are not sufficient to establish a reasonable basis to question the enablement of the present invention. In order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993). MPEP §2164.04.

In the instant case, Skolnick *et al.* describes problems associated with genome-sequencing projects, particularly those associated with determining protein function based on the genome sequences. However, unlike various random sequences discovered by the genome project, ADNF I and ADNF III polypeptide sequences, their biological functions, and their active core site sequences which provide their biological functions are well-known in the art. The specification also provides ample guidance for making other ADNF polypeptides comprising the known active site (*see, e.g.*, pages 17-19 of the specification), and methods for screening suitable ADNF polypeptides for administration. For example, a well-characterized animal model for fetal alcohol syndrome can be used to screen for ADNF polypeptides capable of ameliorating conditions associated with fetal alcohol syndrome. In light of ample guidance provided in the specification, coupled with information known in the art, one of ordinary skill in the art would have been able to make and use other ADNF polypeptides without undue experimentation.

E. The specification provides guidance for delivery of nucleic acids *in vivo*

At page 7 of the Office Action, the Examiner states that "[i]n regard to claim 14, the skilled artisan recognizes that expression of polypeptides from nucleic acid requires the presence of promoter and expression sequences which direct expression in the host. Yet, claim 14 recites administration of a nucleic acid in the absence of such sequences."

Applicants respectfully traverse. Claim 14 recites that "at least one of the ADNF polypeptide is encoded by a nucleic acid which is administered to the subject." Applicants respectfully submit that the language recited in the claim does not limit the claimed method to a delivery of nucleic acids without expression control sequences. The nucleic acid which encodes the ADNF polypeptide can be delivered to the subject on its own or with other expression control sequences. For example, as described at page 25, lines 27-28 of the specification, nucleic acids can be delivered as DNA plasmids, naked nucleic acid, and nucleic acid complexed with a delivery vehicle such as a liposome. The specification further provides various publications well-known in the art that further describes these methodologies (*see, e.g.*, the carryover paragraph of pages 25 and 26). Therefore, the specification provides ample guidance for delivery of nucleic acids that encode ADNF polypeptides.

For the above reasons, the specification provides ample guidance to practice the claimed invention. Accordingly, withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, second paragraph

Claims 1-18 were rejected as allegedly indefinite based on two separate grounds. Each ground of the rejection is addressed separately below.

A. "ADNF", "ADNF I" and "ADNF III"

According to the Examiner, claims 1 and 2 are indefinite in the recitations of "ADNF", "ADNF I", and "ADNF III" because such recitation are neither defined nor readily recognized in the art.

Applicants respectfully traverse this rejection. "[35 U.S.C.] §112, second paragraph, requires a determination of whether those skilled in the art would understand what is claimed in light of the specification." *Orthokinetics v. Safety Travel Chairs Inc.*, 1 USPQ2d 1081 (Fed. Cir. 1986). In the instant case, the terms "ADNF", "ADNF I" and "ADNF III" are clearly defined in the specification in terms of their active core amino acid sequences, molecular weight, pI, and their

biological activities (*see* page 6 of the specification). Therefore, those skilled in the art would understand what is claimed in light of the specification. However, to expedite prosecution, Applicants have amended claim 1 by incorporating the elements of claims 2 and 3, further defining all of ADNF polypeptides in terms of their active core site amino acid sequences. Accordingly, withdrawal of the rejection is respectfully requested.

B. "A combination" and "the ADNF polypeptide"

According to the Examiner, claims 3(c) and claim 12 are indefinite in the recitations of "a combination" and "the ADNF polypeptide," because it is unclear whether Applicants are intending to claim a single peptide which comprises the sequences of SEQ ID NOS:3 and 4, or alternatively, if the intention is to recite a composition comprising a first peptide comprising SEQ ID NO:3 and a second peptide comprising SEQ ID NO:4.

To expedite prosecution, claims 1 and 12 have been amended to recite that "a mixture" of ADNF I and ADNF III polypeptide is being claimed. This amendment clarifies that a mixture of two separate polypeptides is being claimed. Accordingly, withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §102(b)

A. WO96/11948 (Brenneman *et al.*)

Claims 1-6 and 15-18 were rejected as allegedly anticipated by WO96/11948 (Brenneman *et al.*). According to the Office Action, Brenneman *et al.* describes ADNF I polypeptide and administering the peptide nasally at 1 μg/day for alleviation of learning impairment. The Examiner states that this administered dosage is an effective amount to reduce a condition associated with fetal alcohol syndrome including decreased body weight, decreased brain weight, decreased VIP mRNA and death, absent evidence to the contrary. Then the Examiner concludes that because the condition and effective amount are not specified in instant claims and because learning impairment is a condition of fetal alcohol syndrome, the reference anticipates the claimed invention.

Applicants respectfully traverse this rejection. Brenneman *et al.* does not anticipate embodiments of the invention recited in claims 1-6 and 15-18. "For a prior art reference to anticipate in terms of 35 U.S.C. §102, every element of the claimed invention must be identically shown in a single reference." *In re Bond*, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). Here, claims 1-6 and 15-18 are not

anticipated, because every element of claim 1 is not identically shown in Brenneman *et al.* For example, Brenneman *et al.* does not teach, *inter alia*, administering to a subject an ADNF polypeptide, wherein the subject "is exposed to alcohol *in utero*." There is no teaching or suggestion to expose a subject to alcohol *in utero*, let alone administering ADNF polypeptides to the subject. Since every element of the claimed invention is not identically shown in Brenneman *et al.*, Brenneman *et al.* does not anticipate the claimed invention.

As noted by the Examiner, Brenneman *et al.*, at page 27, describes that ADNF I polypeptides can alleviate learning impairment produced by cholinergic blockade. However, the mechanism of learning impairment due to cholinergic blockade (which represents a model for Alzheimer's disease). ADNF I polypeptides were shown to be effective in alleviating learning impairment produced by cholinergic blockade, but there is no teaching or suggestion in Brenneman *et al.* that the ADNF polypeptides can reduce learning impairment of caused by maternal consumption of alcohol, or any other condition associated with fetal alcohol syndrome for subjects who are exposed to alcohol *in utero*. In fact, although Brenneman *et al.* generally teaches the use of ADNF I to treat learning impairment, the finding that ADNF polypeptides can be used to treat conditions associated with fetal alcohol syndrome is surprising. Therefore, Brenneman *et al.* does not anticipate the claimed invention.

B. WO98/35042 (Gozes *et al.*)

Claims 1-3, 7-11 and 15-18 were rejected under 35 U.S.C. §102(a) as allegedly being anticipated by WO98/30452 (Gozes *et al.*). According to the Office Action, Gozes *et al.* describes ADNF III polypeptide and administering the polypeptides to alleviate impaired learning and memory in animals. The Examiner states that this administered dosage is inherently an effective amount to reduce a condition associated with fetal alcohol syndrome including decreased body weight, decreased brain weight, decreased VIP mRNA and death, absent evidence to the contrary. Then the Examiner concludes that because the condition and effective amount are not specified in instant claims and because learning impairment is a condition of fetal alcohol syndrome, the reference anticipates the claimed invention.

Applicants respectfully traverse this rejection. Gozes *et al.* does not anticipate embodiments of the invention recited in claims 1-3, 7-11 and 15-18. "For a prior art reference to anticipate in terms of 35 U.S.C. §102, every element of the claimed invention must be identically shown

in a single reference." *In re Bond*, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). Here, claims 1-3, 7-11 and 15-18 are not anticipated, because every element of claim 1 is not identically shown in Gozes *et al.* For example, Gozes *et al.* does not teach, *inter alia*, administering to a subject an ADNF polypeptide, wherein the subject "is exposed to alcohol *in utero*." There is no teaching or suggestion to expose a subject to alcohol *in utero*, let alone administering ADNF polypeptides to the subject. Since every element of the claimed invention is not identically shown in Gozes *et al.*, Gozes *et al.* does not anticipate the claimed invention.

As noted by the Examiner, Gozes *et al.* describes, at pages 80-81, that ADNF III polypeptides can alleviate learning impairment produced by cholinergic blockade. However, the mechanism of learning impairment due to cholinergic blockade (which represents a model for Alzheimer's disease) is different from the mechanism of learning impairment caused by maternal consumption of alcohol. ADNF III polypeptides were shown to be effective in alleviating learning impairment produced by cholinergic blockade, but there is no teaching or suggestion in Gozes *et al.* that the ADNF polypeptides can reduce learning impairment of caused by maternal consumption of alcohol, or any other condition associated with fetal alcohol syndrome for subjects who are exposed to alcohol *in utero*. In fact, although Gozes *et al.* generally teaches the use of ADNF III to treat learning impairment, the finding that ADNF polypeptides can be used to treat conditions associated with fetal alcohol syndrome is surprising. Therefore, Gozes *et al.* does not anticipate the claimed invention.

C. Taken together, the Examiner's anticipation and enablement rejections with respect to treatment of fetal alcohol syndrome associated learning impairment are improper

The legal relationship between anticipation and enablement is well established. To anticipate an invention, the prior art reference "must enable one skilled in the art to make and use the apparatus or method," before that apparatus or method can be considered anticipated. *See Beckman Instruments Inc. v. LKB Produkter AB*, 13 USPQ2d 1301 at 1304 (Fed. Cir. 1989). The basic question regarding the relationship between enablement and anticipation is whether the prior art is such as to place the invention in the hands of the public, without the benefit of an applicant's disclosure. *See, e.g., In re Brown*, 141 USPQ 245 (C.C.P.A. 1964), and *In re Payne*, (C.C.P.A. 1979) 606 F.2d 303, 314.

On the other hand, for enablement purposes, an application is considered for what it teaches, in combination with the prior art. The Examiner is again reminded that "the test of

enablement is whether one skilled in the art could make or use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation." MPEP 2164.04, citing *United States v. Telectronics, Inc.* 8 USPQ2d 1217 (Fed. Cir. 1988). Indeed, as stated above, "a patent need not teach, and preferably omits, what is well known in the art." *See Spectra-Physics, Inc. v. Coherent, Inc.,* 3 USPQ2d 1737 (Fed. Cir. 1987). Before an application can be non-enabling, the application, in combination with everything that is known in the prior art must not teach how to practice the invention.

As described above, the Examiner has rejected the claims as anticipated by Brenneman *et al.* and Gozes *et al.*, which teach administration of ADNF polypeptides to treat learning impairment. The Examiner has also rejected the claims as lacking enablement for the treatment of fetal alcohol conditions such as compromises in learning, memory and adaptive responses.

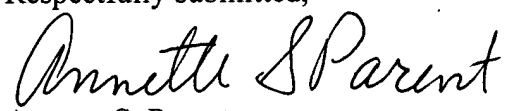
It should be immediately apparent that there is no way that an invention can be both anticipated and not enabled. To be anticipated, the prior art reference, even without the benefit of an applicants disclosure, must teach one of skill how to practice the invention. To not be enabled, the application, in combination with the prior art, must not teach one of skill how to practice the invention. It is simply not possible for Gozes *et al.* or Brenneman *et al.* to teach one of skill how to practice the invention, while Gozes *et al.* or Brenneman *et al.* + the present application do not. In essence, the Examiner's argument is that one of skill would not known whether the invention works, or how to practice it, but that, if it does work and if one of skill did know how to practice it, it would be anticipated. This logical non sequitur has been disapproved by the Federal Circuit. *See In re Dow Chemical*, 5 USPQ2d 1529, 1531 (Fed Cir. 1988).

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A method for reducing a condition associated with fetal alcohol syndrome in a subject who is exposed to alcohol *in utero*, the method comprising administering to the subject an ADNF polypeptide in an amount sufficient to reduce the condition associated with fetal alcohol syndrome, wherein the ADNF polypeptide is a member selected from the group consisting of:

(a) an ADNF I polypeptide having the following amino acid sequence:

$(R^1)_x$-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala-$(R^2)_y$ (SEQ ID NO:3);

(b) an ADNF III polypeptide having the following amino acid sequence:

$(R^3)_w$-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln-$(R^4)_z$ (SEQ ID NO:4);

(c) a mixture of the ADNF I polypeptide of part (a) and the ADNF III polypeptide of part (b);

wherein R^1, R^2, R^3, and R^4 are independently selected and are an amino acid sequence comprising from 1 to about 40 amino acids wherein each amino acid is independently selected; and

x, y, w, and z are independently selected and are equal to zero or one;

(d) a full length ADNF I polypeptide which comprises Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala;

(e) a full length ADNF III polypeptide which comprises Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln; and

(f) a mixture of a full length ADNF I polypeptide of part (d) and a full length ADNF III polypeptide of part (e).

2. (Amended) The method of claim 1, wherein the ADNF polypeptide is a member selected from the group consisting of [a] the full length ADNF I polypeptide, [a] the full length ADNF III polypeptide, and [a combination] the mixture of [a] the full length ADNF I polypeptide and [a] the full length ADNF III polypeptide.

3. (Amended) The method of claim 1, wherein the ADNF polypeptide is a member selected from the group consisting of:

(a) [an] the ADNF I polypeptide having the following amino acid sequence:

$(R^1)_x$-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala-$(R^2)_y$ (SEQ ID NO:3);

(b) [an] the ADNF III polypeptide having the following amino acid sequence:

$(R^3)_w$-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln-$(R^4)_z$ (SEQ ID NO:4); and

(c) [a combination] the mixture of the ADNF I polypeptide of part (a) and the ADNF III polypeptide of part (b);

wherein R^1, R^2, R^3, and R^4 are independently selected and are an amino acid sequence comprising from 1 to about 40 amino acids wherein each amino acid is independently selected; and

x, y, w, and z are independently selected and are equal to zero or one.

12. (Amended) The method of claim [3] 1, wherein the ADNF polypeptide is a [combination] mixture of ADNF I polypeptide of part (a) and the ADNF III polypeptide of part (b).

APPENDIX B

PENDING CLAIMS CURRENTLY UNDER EXAMINATION

1. (Amended) A method for reducing a condition associated with fetal alcohol syndrome in a subject who is exposed to alcohol *in utero*, the method comprising administering to the subject an ADNF polypeptide in an amount sufficient to reduce the condition associated with fetal alcohol syndrome, wherein the ADNF polypeptide is a member selected from the group consisting of:

(a) an ADNF I polypeptide having the following amino acid sequence:

$(R^1)_x$-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala-$(R^2)_y$ (SEQ ID NO:3);

(b) an ADNF III polypeptide having the following amino acid sequence:

$(R^3)_w$-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln-$(R^4)_z$ (SEQ ID NO:4);

(c) a mixture of the ADNF I polypeptide of part (a) and the ADNF III polypeptide of part (b);

wherein R^1, R^2, R^3, and R^4 are independently selected and are an amino acid sequence comprising from 1 to about 40 amino acids wherein each amino acid is independently selected; and

x, y, w, and z are independently selected and are equal to zero or one;

(d) a full length ADNF I polypeptide which comprises Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala;

(e) a full length ADNF III polypeptide which comprises Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln; and

(f) a mixture of a full length ADNF I polypeptide of part (d) and a full length ADNF III polypeptide of part (e).

2. (Amended) The method of claim 1, wherein the ADNF polypeptide is a member selected from the group consisting of the full length ADNF I polypeptide, the full length ADNF III polypeptide, and the mixture of the full length ADNF I polypeptide and the full length ADNF III polypeptide.

3. (Amended) The method of claim 1, wherein the ADNF polypeptide is a member selected from the group consisting of:

(a) the ADNF I polypeptide having the following amino acid sequence:

$(R^1)_x$-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala-$(R^2)_y$ (SEQ ID NO:3);

(b) the ADNF III polypeptide having the following amino acid sequence:

$(R^3)_w$-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln-$(R^4)_z$ (SEQ ID NO:4); and

(c) the mixture of the ADNF I polypeptide of part (a) and the ADNF III polypeptide of part (b);

wherein R^1, R^2, R^3, and R^4 are independently selected and are an amino acid sequence comprising from 1 to about 40 amino acids wherein each amino acid is independently selected; and

x, y, w, and z are independently selected and are equal to zero or one.

4. (as filed) The method of claim 3, wherein for the ADNF I polypeptide x and y are both zero.

5. (as filed) The method of claim 3, wherein for the ADNF I polypeptide:

x is one;

R^1 is Val-Leu-Gly-Gly-Gly (SEQ ID NO:5); and

y is zero.

6. (as filed) The method of claim 3, wherein for the ADNF I polypeptide:

x is one;

R^1 is Val-Glu-Glu-Gly-Ile-Val-Leu-Gly-Gly-Gly (SEQ ID NO:6);

and

y is zero.

7. (as filed) The method of claim 3, wherein for the ADNF III polypeptide w and z are both zero.

8. (as filed) The method of claim 3, wherein for the ADNF III polypeptide:

w is one;

R^3 is Gly-Gly; and

z is zero.

9. (as filed) The method of claim 3, wherein for the ADNF III polypeptide:
w is one;
R^3 is Leu-Gly-Gly;
z is one; and
R^4 is Gln-Ser.

10. (as filed) The method of claim 3, wherein for the ADNF III polypeptide:
w is one;
R^3 is Leu-Gly-Leu-Gly-Gly (SEQ ID NO:7);
z is one; and
R^4 is Gln-Ser.

11. (as filed) The method of claim 3, wherein for the ADNF III polypeptide:
w is one;
R^3 is Ser-Val-Arg-Leu-Gly-Leu-Gly-Gly (SEQ ID NO:8);
z is one; and
R^4 is Gln-Ser.

12. (Amended) The method of claim 1, wherein the ADNF polypeptide is a mixture of ADNF I polypeptide of part (a) and the ADNF III polypeptide of part (b).

13. (as filed) The method of claim 3, wherein x, y, w, and z are all zero.

14. (as filed) The method of claim 3, wherein at least one of the ADNF polypeptide is encoded by a nucleic acid which is administered to the subject.

15. (as filed) The method of claim 1, wherein the condition is a decreased body weight of the subject.

16. (as filed) The method of claim 1, wherein the condition is a decreased brain weight of the subject.

17. (as filed) The method of claim 1, wherein the condition is a decreased level of VIP mRNA of the subject.

18. (as filed) The method of claim 1, wherein the condition is death of the subject *in utero*.